An Essential Role of Variant Histone H3.3 for Ectomesenchyme Potential of the Cranial Neural Crest.

Journal: PLoS Genet

Publication Year: 2012

Authors: Samuel G Cox, Hyunjung Kim, Aaron Timothy Garnett, Daniel Meulemans Medeiros, Woojin An, J Gage Crump

PubMed link: 23028350

Funding Grants: Skeletogenic Neural Crest Cells in Embryonic Development and Adult Regeneration of the Jaw, CIRM Stem Cell Biology Training Grant

Public Summary:
The evolution of the vertebrate head was made possible in large part by the emergence of a new cell population, the cranial neural crest. These cells contribute to diverse structures of the head, including most of the skull, yet how neural crest cells acquire such broad potential during development has remained a mystery. By studying mutant zebrafish that lack the neural-crest-derived skull, we find that the unusual potential of these cells depends on an “H3.3” version of one of the histone proteins that package their DNA. We propose then that a dramatic change in the packaging of DNA is a key step in allowing crest cells to make a wide range of new cell types in the vertebrate head.

Scientific Abstract:
The neural crest (NC) is a vertebrate-specific cell population that exhibits remarkable multipotency. Although derived from the neural plate border (NPB) ectoderm, cranial NC (CNC) cells contribute not only to the peripheral nervous system but also to the ectomesenchymal precursors of the head skeleton. To date, the developmental basis for such broad potential has remained elusive. Here, we show that the replacement histone H3.3 is essential during early CNC development for these cells to generate ectomesenchyme and head pigment precursors. In a forward genetic screen in zebrafish, we identified a dominant D123N mutation in h3f3a, one of five zebrafish variant histone H3.3 genes, that eliminates the CNC-derived head skeleton and a subset of pigment cells yet leaves other CNC derivatives and trunk NC intact. Analyses of nucleosome assembly indicate that mutant D123N H3.3 interferes with H3.3 nucleosomal incorporation by forming aberrant H3 homodimers. Consistent with CNC defects arising from insufficient H3.3 incorporation into chromatin, supplying exogenous wild-type H3.3 rescues head skeletal development in mutants. Surprisingly, embryo-wide expression of dominant mutant H3.3 had little effect on embryonic development outside CNC, indicating an unexpectedly specific sensitivity of CNC to defects in H3.3 incorporation. Whereas previous studies had implicated H3.3 in large-scale histone replacement events that generate totipotency during germ line development, our work has revealed an additional role of H3.3 in the broad potential of the ectoderm-derived CNC, including the ability to make the mesoderm-like ectomesenchymal precursors of the head skeleton.